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The Relation Between Prescription Drug Usage and Cognitive Performance in Later Life

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Abstract
Older adults, the primary consumers of prescription medications in the United States, may be particularly prone to medication side effects. The present study examined the relation between change in prescriptions and change in cognitive performance (i.e., inductive reasoning and everyday problem solving), as well as how three common classes of medication (i.e., cardiovascular, hormone/synthetic substitutes, and central nervous system agents) were related to cognitive performance. Data were collected from 78 community-dwelling older adults (M = 71.14 years, SD = 5.35) over an 18-month period. Results indicated that types of drugs were differentially related to cognitive change and that the total number of prescriptions was related to change in cognitive performance. Clinical and research advantages of using specific cognitive and prescription assessments, rather than more global measures, are discussed.

Keywords
Prescription medication, cognitive change, cognitive training

Disciplines
Family, Life Course, and Society

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ABSTRACT. Older adults, the primary consumers of prescription medications in the United States, may be particularly prone to medication side effects. The present study examined the relation between change in

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prescriptions and change in cognitive performance (i.e., inductive reasoning and everyday problem solving), as well as how three common classes of medication (i.e., cardiovascular, hormone/synthetic substitutes, and central nervous system agents) were related to cognitive performance. Data were collected from 78 community-dwelling older adults ($M = 71.14$ years, $SD = 5.35$) over an 18-month period. Results indicated that types of drugs were differentially related to cognitive change and that the total number of prescriptions was related to change in cognitive performance. Clinical and research advantages of using specific cognitive and prescription assessments, rather than more global measures, are discussed.

KEYWORDS. Prescription medication, cognitive change, cognitive training

INTRODUCTION

Although older adults make up only 13% of the population in the United States, adults aged 65 and older use approximately 30% of prescription medications (American Association of Retired Persons Administration on Aging, 1999). Research has found that nearly 79% of older adults report taking at least one prescription drug, with 10% of older adults aged 65 to 74 years reporting at least five prescriptions, and 15% of adults aged 75 years and older reporting five or more prescriptions (Chen, Dewey, & Avery, 2001). Due to the growing population of adults over the age of 65 and the high percentage of older adults who are prescribed medications, understanding the potential effects of these medications constitutes a major health concern. One area of particular significance is the relation between medications and cognitive functioning in later life.

Relation Between Prescription Drug Usage and Cognitive Performance in Later Life

Improved understanding of the relation between prescriptions and cognitive functioning is vital, given the prevalence of medication usage and resulting cognitive side effects (Meador, 1998), coupled with normative cognitive declines (Schaie, 1996). Increasing evidence suggests that medication-induced cognitive impairment is often mistaken for "normal" or age-related declines, and thus is often ignored or left untreated. For example, research examining older adult hospital patients found that prescription drugs were the cause of 11% to 30% of reported cases of delirium (Francis, Martin, & Kapoor, 1990; O'Keefe & Lavan, 1999) and 2% to 12% of reported cases of dementia (Larson, Kukull, Buchner, & Reifler, 1987; Starr & Whalley, 1994). The use of anticholinergic agents has been strongly associated with both delirium and reversible dementia, particularly if an individual is taking multiple anticholinergic drugs (Tollefson, Montague-Clouse, & Lancaster, 1991).

In general, taking multiple prescription medications (i.e., polypharmacy) has been identified as a risk factor for developing drug-induced cognitive impairment due to the cumulative effects of each drug as well as potential drug interactions. Starr and colleagues (2004) found that greater prescription use reported by 478 nondemented survivors of the 1932 Scottish Mental Health Survey was related to a decline in intelligence test performance from age 11 to age 80. Factors that increase susceptibility to polypharmacy negative effects include gender (females are more likely to be taking multiple medications; Chen et al., 2001), increased age (Williams, 2002), and the presence of cognitive impairment due to other causes (Meador, 1998; Mulsant et al., 2003).

Gaining a further understanding of the side effects of polypharmacy is important not only for clinicians, but also for researchers, who must consider the possible effects of multiple prescription drugs on cognitive performance and the ensuing implications for study results and recommendations. As much of the research on the effects of polypharmacy has used data from institutionalized or hospitalized patients, it is important to determine how the number of prescribed medications influences the cognitive performance of relatively healthy, community-dwelling older adults. For this reason, the prescription drug use of well elders was examined in the present study.

Medication Class and Varying Effects on Cognitive Performance

Examining the potential effects of medication *type* may also be beneficial to further explicate the relation between prescriptions and the maintenance or loss of cognitive abilities. The current study focused on cardiovascular drugs, hormone/synthetic substitutes, and central nervous system agents due to the prevalence of these drugs in the older adult population (Johnson & Moore, 1988), as well as their documented relation to cognition (see Berg & Dellasega, 1996; Gupta & Aronow, 2002).

Research suggests that cardiovascular drugs (e.g., antihypertensives) tend to have a protective effect on cognitive ability by reducing the negative effects of health conditions such as hypertension, which can affect visual memory, abstract reasoning, and attention (e.g., Andre-Petersson, Hagberg, Janzon, & Steen, 2001). For example, Murray, Lane, and Gao (2002) found that the use of antihypertensive, antihyperlipidemic (i.e., medications meant to decrease triglyceride and low-density lipoprotein levels), or antiplatelet (i.e., drugs meant to reduce or inhibit blood clotting) medications reduced the likelihood of dementia by approximately 40% in a sample of community-dwelling older Black adults. Longitudinal studies also support the protective benefits of antihypertensive medications (e.g., Launer & Masaki, 1995).

Research examining the effects of hormones and other synthetic substitutes on cognition has been equivocal. For example, Resnick, Metter, and Zonderman's (1997) results support a protective role of estrogen on women's cognitive abilities. However, Shumaker and colleagues (2003) found that older women taking estrogen and progestin were actually at a higher risk for developing dementia. The effect of hormones and synthetic substitutes on the cognitive performance of males is also unclear. Janowsky, Chavez, and Orwoll (2000) found that older males taking testosterone supplements scored higher on working memory tasks compared with older males taking a placebo. However, as Asthana (2003) points out, the equivocal results of these studies may be due to the employment of cognitive measures that are too global, and the effects of prescribed medications may be more salient in specific cognitive domains (e.g., Duka, Tasker, & McGowan, 2000). Both points relate to the current study.

The third class of drug examined in the present study was central nervous system (CNS) agents, which included such medications as hypnotics and sedatives, analgesics, and psychotropic agents. Berg and Dellasega (1996) found that the use of psychotropic drugs had a significant and cumulative negative effect on verbal ability, spatial relations, and picture recognition. In addition, McShane and colleagues (1997) found that patients with dementia who were taking psychotropic drugs displayed a decrease in cognitive performance twice that of a sample not taking psychotropic medication. Likewise, hypnotics such as benzodiazepines, as well as anticonvulsants have been related to decreased cognitive functioning in older adults (Moore & O'Keeffe, 1999).

Study Rationale

The present study sought to further the understanding of the relation between change in cognition and change in medications in a sample of community-dwelling older adults. This study used specific cognitive measures (i.e., inductive reasoning and everyday problem solving) to more finely examine the potential association between medication and cognition in terms of both the number of prescriptions older adults report and the specific medication classes. Inclusion of an everyday problem-solving measure addressed a dimension of cognition that has not been previously examined in relation to medications in a population of community-dwelling older adults. This is important, as everyday problem-solving measures are likely more predictive of functional ability than are basic cognitive measures (Allaire & Marsiske, 2002).

Two methodological advantages of this study should also be noted. First, because of the longitudinal nature of this study, the relation between *change* in the number of prescriptions (and specific prescription classes) and *change* in cognitive performance can be assessed. Second, this study used the medication "brown bag" method to collect data on the number and type of prescriptions, which enables the researcher to check the information for each medication as recorded on the actual medication bottle (e.g., Caskie, Willis, Schaie, & Zanjani, 2006). While this method does not necessarily mean that participants are actually taking the medication properly, it does present the advantage that researchers do not need to rely solely on self-reported data.

METHOD

The older adults in this study were recruited to participate in a cognitive training protocol designed to improve inductive reasoning and to compare the effects of individual versus collaborative training with a spouse. The training consisted of 10 sessions, the majority of which were completed by participants in their own home. Current study procedures related to random group assignment, administration of training materials, and follow-up assessments correspond to prior cognitive training research (Ball et al., 2002; Willis & Schaie, 1994; more detailed information is available in Saczynski, Margrett, & Willis, 2004, and Margrett & Willis, 2006). It is important to note, however, that study advertisements and descriptions did not target persons with cognitive impairments (e.g., this was not advertised as a program to treat or enhance cognitive performance) and such individuals were excluded from participation during screening. Use of this particular sample allowed us to examine the relative importance of prescribed medication within a cognitive training paradigm.

Participants

Participants were part of a convenience sample recruited through local media and community organizations. The sample included 106 older adults who were screened prior to study enrollment to ensure that the participants were community-dwelling and reported no limitations in self-care activities. Out of this original sample, 78 participants (40 females and 38 males) had complete medication data at baseline and the 18-month follow-up. Analyses found no significant differences in age, education, or number of medications at baseline between the participants that were included in the present analyses and those who were not included.

The mean age of the final sample ($N = 78$) at baseline was 71.14 years ($SD = 5.35$; range = 61 to 83 years). The average educational level was 16.09 years ($SD = 3.05$; range = 12 to 22 years) with 76% of participants reporting an educational level of more than twelve years. The median yearly income was $47,644 (range = $18,000 to $50,000+). All participants resided in rural central Pennsylvania and were White.

Procedure

Due to the nature of the larger training study, older married couples were recruited and screened for eligibility during a brief phone interview (for a similar study, see Margrett & Marsiske, 2002). The screening criteria were: (a) 60 years of age or older; (b) no self-reported limitations in activities of daily living (i.e., bathing, dressing, personal hygiene; Katz, Ford, Moskowitz, Jackson, & Jaffee, 1963); and (c) a minimal marital duration of at least 15 years (Carstensen, Levenson, & Gottman, 1995). Although couples were originally recruited for the larger study, the current analysis includes data from *individuals* who had complete data (i.e., both partners did not have to have complete data for one spouse to be included in the current analyses). At the study start, both spouses within a couple were randomly assigned to one of three training conditions and those respondents included in the current analyses were assigned as following: (1) Individual Training group ($n = 22$ individuals), (2) Collaborative Training group ($n = 26$ individuals), and (3) Questionnaire Only (control) group ($n = 30$ individuals).

All participants signed an informed consent form and were treated in accordance to the ethical guidelines set forth by the American Psychological Association (2002). Couples received compensation for parking and a small honorarium based on their hours of effort (i.e., $40 for the two training groups and $20 for the nontraining group).

Pretest and Posttest Assessments

The analyses reported in the current study focus on the baseline and an 18-month follow-up assessment. The first assessment occasion was a 3-hour group baseline assessment conducted immediately prior to cognitive training. The second assessment was a delayed posttest that was conducted 18 months after the baseline session. During both assessments, participants completed the Letter Series Test (Blieszner, Willis, & Baltes, 1981), the Everyday Problems Test (EPT; Willis & Marsiske, 1997), and a demographic measure. Participants in all three treatment groups were assessed under the same conditions—at a community or university setting, in small groups with a trained proctor. Spouses participated in the pretest and post-test assessments together. Each group testing session contained a *combination* of 2 to 3 couples from each of the three treatment conditions. Testing was arranged in this manner in order to prevent testing of only one treatment condition at a time which could conceivably affect testing outcome (e.g., tester bias, altered group dynamics). The length of time between pre- and posttests was consistent across the three groups.

Reasoning Training Protocol

The training protocol used in the current study was based on prior work by Willis (e.g., Ball et al., 2002; Willis & Schaie, 1994). Information was presented in workbook form, and the training consisted of ten sessions designed to introduce and reinforce inductive reasoning strategies helpful in determining patterns needed to navigate daily life (e.g., compiling a medication chart). The training materials utilized both basic series (e.g., letter, words) as well as stimuli common to everyday life (e.g., transportation schedule). The training was expected to improve performance on inductive reasoning measures.

Training consisted of 10 sessions that were completed over a four to 5-week period. Sessions consisted of the introduction of five strategies to improve inductive reasoning performance (e.g., underline repeated elements, insert a slash between pattern repetitions) and opportunities to practice inductive reasoning on elementary items (e.g., letter and word series) and items of a practical nature (e.g., transportation schedule). After the initial session, training occurred in participants' homes. Participants in the Individual group completed all materials individually, without assistance from their spouse. In contrast, trainees in the Collaborative group completed all sessions with their spouse. Participants assigned to the Control group completed the same pre/posttests as the training groups, but did not receive training.

Measures

Letter Series Test

To assess inductive reasoning ability, participants completed the Letter Series Test (Blieszner et al., 1981). This 20-item timed measure gauged respondents' ability to identify the pattern in a series of letters and to generate the next letter in each series. This measure displays good internal reliability ($\alpha = 0.91$; Blieszner et al.) and test-retest reliability ($r = 0.84$; Schaie, Dutta, & Willis, 1991). In terms of validity, this measure was related to everyday problem solving (Cornelius & Caspi, 1987) and other tests of inductive reasoning (e.g., word series; Willis & Schaie, 1986). Change scores were calculated by subtracting the number of correct items at baseline from the number of correct items at the 18-month posttest; thus, positive change scores indicated an increase in performance. Results indicated a significant increase in performance at Time 2 (range = –4 to 8; see Table 1), with the training conditions improving significantly more than the control condition. Thus, condition was entered in all of the analyses.

TABLE 1. Sample descriptive information ($N = 78$)

Variable	Baseline		18-month Posttest		Statistical Tests	
	Mean (*SD*)	Range	Mean (*SD*)	Range	*t*	*p*
Health-related Information						
Self-rated physical health	2.48 (0.77)	1–5	2.65 (1.10)	1–6	–1.60	0.11
Hospital visits (days within last six months)	0.47 (1.37)	0–10	1.90 (0.31)	1–2	–8.38	<0.01
Average number of prescriptions	2.73 (2.27)	0–8	3.40 (2.24)	0–8	–3.06	0.03
Cognitive Performance						
Everyday Problems Test	31.39 (6.42)	11–41	31.29 (6.74)	11–42	–0.24	0.80
Letter Series Test	8.38 (3.21)	1–16	9.69 (3.68)	1–20	4.63	<0.01
	n	%	n	%		
Reported Prescriptions within Drug Category						
Cardiovascular only	16	20.5%	16	20.5%		
Hormone/Synthetic only	10	12.8%	10	12.8%		
Central nervous system agent only	3	3.8%	3	3.8%		
Combination of categories	28	35.9%	28	35.9%		
No prescriptions from three study categories	21	26.9%	21	26.9%		

Everyday Problems Test

The Everyday Problems Test (EPT) (Willis & Marsiske, 1997) was designed to assess older adults' ability to solve problems in seven critical everyday domains (i.e., Instrumental Activities of Daily Living; Lawton & Brody, 1969), such as health and financial management. A 42-item open-ended version of the test was used. Participants were presented with a stimulus (e.g., a Medicare chart) and asked to solve age-relevant problems (e.g., calculating the Medicare portion of a hospital stay). This measure displayed good internal consistency in past research (alphas ranging from 0.62 to 0.74 for the subscales and 0.94 for the entire scale) and high test-retest stability (.91 for entire scale; Marsiske & Willis, 1995). In addition, Whitfield, Baker-Thomas, Heyward, Gatto, and Williams (1999) found the EPT to be related to measures of fluid intelligence (e.g., inductive reasoning). Change scores were calculated by subtracting the number of correct items at the 18-month post-test from the number correct at baseline. The average EPT change from Time 1 to Time 2 was not significant (range = –9 to 8; see Table 1). Although there were not overall changes in means on the EPT between Time 1 and Time 2, it was decided that predictors of change were still important, given the variability in performance and the relation between basic cognitive measures and everyday cognitive measures (Marsiske & Willis, 1995).

Prescription Medication Data

Prescription data were collected using the "brown bag" method as used in the Seattle Longitudinal Study (see Caskie,Willis, Schaie, & Zanjani, 2006), which entailed older adults bringing their medications with them to the testing session (Caskie,Willis, Schaie, & Zanjani, 2006). Information including the name of the medication, dosage, and most recent refill date was recorded by the test administer. Following testing, prescriptions were then coded by trained research assistants supervised by the first and second authors. Prescriptions were double-coded, and if a discrepancy was found, the coders referred to the raw data to determine the correct classification based on the reported indication when available. This classification was then checked by the first and/or second authors. Discrepancies between coders were minimal. Each medication received an American Hospital Formulary Service (AHFS, 2004) code, which classified medications according to increasingly specific categories (e.g., Level One: cardiovascular; Level Two: beta-blocker). The present study used the major drug classification specified at level one. While using this broad classification scheme does not provide information regarding the effects of specific prescription medications, this strategy does provide information regarding the effects of specific categories of medications on specific assessments of cognitive performance. These results can then be used to inform future research on the effects of more specific classes of medications.

For the prescription drug data, an initial baseline was collected immediately after cognitive training. At this time, participants were asked to report any medication changes since the study inception 7 to 8 weeks prior. The majority of participants (88.5%) reported no changes in medication usage during that interval, with an additional 7.5% reporting adding one medication, 1.25% reporting dropping a medication, and 2.75% reporting an increase of two medications or more. The number of medications reported at the immediate follow-up was adjusted according to participants' reports. This resulted in a baseline indicator (e.g., if four medications were reported at the immediate follow-up and one medication was added in the period between baseline and the immediate follow-up, the adjusted baseline score was three medications). Eighteen-month change scores were calculated by subtracting the adjusted number of total medications at baseline from the number of prescriptions recorded at the 18-month posttest (see Table 1). Overall, participants reported taking more medications at Time 2 compared to Time 1, with the change in the number of prescriptions ranging from –4 to 6. Although the difference between Time 1 and Time 2 data was statistically significant, the practical significance of this slight increase likely depends on the type of medication(s) being added. This suggests that number of drugs, per se, may not possess adequate specificity when examining the relation between prescription medications and cognition. Thus, number of medications *and* medication class was examined in the present study.

Health Information

As part of a pre-session homework package, participants completed a paper-and-pencil demographic measure that included items assessing self-reported ratings of physical health and number of hospital visits within the past 6 months. Current physical health compared to health at 20 years of age was indicated on a scale from 1 (*Very Good*) to 6 (*Very Poor*). As shown in Table 1, analyses indicated that the number of hospital visits reported for the previous 6 months increased from Time 1 to Time 2, but self-rated physical health did not change from Time 1 to Time 2. There were no statistically significant differences between the training and control conditions on the number of hospital visits, self-rated health, scores on the EPT, or scores on the Letter Series Test at Time 1 or at Time 2.

RESULTS

The following analyses focused on the predictive utility of medication usage in relation to change in performance on the Letter Series Test (Blieszner et al., 1981) and Everyday Problems Test (Willis & Marsiske, 1997) over an 18-month interval. Both the type of medications and the change in the number of medications were examined as predictors. Prior to these analyses, general descriptive statistics regarding group differences and overall prescription usage are reported (i.e., total number of prescriptions and percentage reporting prescriptions from the three most common drug classes: CNS agents, cardiovascular drugs, and hormone/synthetic substitutes). Initial analyses identified a potential outlier who reported a large change in the number of hospital visits from Time 1 to Time 2; however, the pattern of results remained consistent regardless of whether this outlier were included or not. Thus, the following results are based on data from the entire sample ($N = 78$).

Descriptive Statistics

Overall, 80% of the sample reported taking at least one prescription drug. Of the participants who reported a prescription from the categories of interest in this study, results indicated that approximately 28% reported taking only cardiovascular drugs, 5% reported taking only CNS agents, 18% reported taking only hormone/synthetic substitutes, and 49% reported prescriptions from two or more of these categories (see Table 2 for detailed description of particular types of drugs under each main AHFS category). Additionally, 25% of participants reported a combination of prescriptions from these three drug categories and prescriptions that did not fall under the three studied categories (e.g., a cardiovascular drug and an anti-infective agent).

An examination of group differences in the use of the specific classes of prescription medications at Time 1 indicated that females were more likely to report taking hormone/synthetic substitutes (28%) compared with males (9%), χ^2 $(1, N = 78) = 9.84$, $p < 0.01$, and that females were more likely to report taking CNS agents (25%) compared to males (10%),

TABLE 2. Number and type of prescription medications included under primary AHFS categories

Drug Type	Time 1		Time 2	
	N	%	*N*	%
Cardiovascular	75		86	
Cardiac drugs	2	2.7	1	1.2
Antilipemic agents	22	29.3	23	26.7
Hypotensive agents	35	46.7	33	38.4
Vasodilating agents	6	8.0	2	2.3
Alpha adrenergic blocker	0	0.0	5	5.8
Beta adrenergic blockers	10	13.3	11	12.8
Calcium-channel blockers	0	0.0	3	3.5
Renin-angiotensin-aldosterone system inhibitors	0	0.0	8	9.3
Central Nervous System Agents	24		26	
Analgesics and antipyretics	8	37.5	10	38.5
Anticonvulsants	2	4.2	2	7.7
Psychotherapeutic agents	11	37.5	10	30.8
Anxiolytics, sedatives, and hypnotics	3	8.3	4	15.4
Hormones & Synthetic Substitutes	38		35	
Adrenals	0	0.0	4	11.4
Estrogens & antiestrogens	11	28.9	10	28.6
Antidiabetic agents	5	13.2	3	8.6
Parathyroid	0	0.0	2	5.7
Progestins	5	13.2	3	8.6
Other corpus luteum hormones	5	13.2	3	8.6
Thyroid and antithyroid agents	12	31.6	10	28.6

Note. The listed drug types reflect only those that were reported by participants and are not a comprehensive list of all types of prescriptions under each category (note that participants may have reported multiple prescriptions in any given category).

χ^2 (1, N = 78) = 4.53, $p < 0.05$. Males (40%) and females (32%) did not differ significantly in the likelihood of taking a cardiovascular drug. With regard to the treatment groups, there were no significant differences in terms of age, number of medications, types of medications, number of hospital visits, or self-rated physical health. Possible baseline differences between participants who reported a prescription from at least one of the studied categories and those who did not were explored using a series of *t*-tests. Results indicated that these groups did not differ in terms of performance on the cognitive tasks, number of hospital visits, age, or self-rated physical health.

Change in Number of Medications and Change in Cognitive Performance

Hierarchical multiple regression analysis was conducted to examine the relation between change in number of prescription medications and change in cognitive performance (i.e., Letter Series Test and Everyday Problems Test). Several additional predictor variables hypothesized to be related to cognitive performance were entered into the model. The four regression steps included: (a) demographics (age, sex, educational attainment), (b) training condition and baseline performance on the respective cognitive task, (c) health indicators (change in self-rated health and change in hospital visits from baseline to 18-month post-test), and (d) change in number of reported prescription medications (18-month post-test – baseline).

First, a hierarchical multiple regression was performed to examine the relation between the change in the number of medications reported and the change in performance on the Letter Series Test (Blieszner et al., 1981). As shown in Table 3, results indicated that the demographic variables did not significantly contribute to the prediction of change in performance. The addition of step two (training condition and baseline performance) did significantly increase the amount of explained variance. The addition of step three (health indicators) did not significantly increase the amount of explained variance. Inclusion of step four (change in number of medications) did significantly increase the amount of explained variance. The overall model accounted for a significant portion of the variance in change in performance on the Letter Series measure ($R^2 = 0.21$, $p < 0.05$).

Results of the hierarchical multiple regression analysis examining change in performance on the EPT (Willis & Marsiske, 1997) were similar to the previous analysis (see Table 3). Once again, steps one (demographics) and three (health indicators) did not explain a significant amount of variance in change in EPT performance. However, the addition of steps 2 (training condition and baseline performance) and step 4 (change in number of medications) significantly increased the amount of explained variance. The overall model accounted for 21.5% of the variance in performance on the EPT ($p < 0.05$).

Results from these regression analyses suggest that an increase in the number of reported prescriptions was positively related to change scores on both the inductive reasoning task and the everyday problem-solving task. Age, baseline EPT scores, change in hospital visits, and change in

TABLE 3. Results of hierarchical regression analyses examining total number of reported prescriptions

Predictor	Letter Series Test				Everyday Problems Test			
	ΔR^2	B	$SE\ B$	β	ΔR^2	B	$SE\ B$	β
Step 1	0.02				0.02			
Age		−0.02	0.06	−0.06		−0.16	0.07	−0.25*
Education		0.11	0.10	0.13		0.11	0.16	0.09
Sex		0.43	0.60	0.09		−0.18	0.90	−0.02
Step 2	0.10*				0.08*			
Training condition		0.60	0.34	0.19		0.29	0.50	0.06
Baseline cognitive score		−0.17	0.10	−0.22		−0.16	0.07	−0.27*
Step 3	0.02				0.06			
Change in hospital visits		0.25	0.19	0.15		−0.60	0.28	−0.24*
Change in self-rated physical health		−0.01	0.30	−0.03		0.01	0.46	0.01
Step 4	0.07**				0.05**			
Change in total number of prescriptions		0.34	0.14	0.26*		0.44	0.21	0.23**
Total R^2	0.21*				0.21*			
Total F	$(8, 71) = 2.22, p < 0.05$				$(8, 71) = 2.35, p < 0.05$			

Note. $^*p < 0.05$, $^{**}p < 0.01$.

total number of prescriptions were predictive of change in everyday problem-solving performance.

Category of Medication and Change in Cognitive Performance

The next series of analyses examined the relations between the reported use of cardiovascular drugs, hormone/synthetic substitutes, and CNS agents at baseline and 18-month change in performance on the two cognitive measures. A series of 2 (Drug: Taking or Not Taking Medication) × 2 (Sex: Male, Female) × 3 (Training Condition: Control, Individual, Collaborative) analyses of covariance (ANCOVA) tests was performed (covarying education and age) for each cognitive task and prescription category (see Table 4).

Prior to performing these analyses, we examined the stability of prescription use between the baseline assessment occasion and the 18-month post-test in terms of whether participants were taking or not taking drugs within the 3 categories of interest (e.g., taking a cardiovascular drug at

TABLE 4. Analyses examining the relation between change in number of prescriptions and change on cognitive measures

Source	Letter Series Test			Everyday Problems Test		
	df	*MS*	*F*	*df*	*MS*	*F*
Cardiovascular Drugs						
Age (covariate)	1	0.01	0.01	1	15.82	0.62
Education (covariate)	1	0.01	0.02	1	4.22	0.31
Cardiovascular Drug (CD)	1	1.47	0.23	1	67.64	4.97*
Training Condition (TC)	2	15.56	2.42	2	3.57	0.26
Sex (S)	1	5.09	0.79	1	4.97	0.37
CD X TC	2	4.41	0.69	2	29.60	2.17
CD X S	1	0.72	0.11	1	28.47	2.09
TC X S	2	3.16	0.49	2	4.47	0.33
CD X TC X S	2	1.62	0.25	2	6.19	0.45
Central Nervous System Agents						
Age (covariate)	1	1.03	0.19	1	28.74	1.99
Education (covariate)	1	0.35	0.06	1	2.59	0.18
Central Nervous System Agent (CNS)	1	2.09	0.37	1	0.02	0.01
Training Condition (TC)	2	7.95	1.42	2	5.98	0.42
Sex (S)	1	6.45	1.15	1	22.38	1.56
CNS X TC	2	14.24	2.54	2	6.05	0.42
CNS X S	1	8.67	1.55	1	68.46	4.75*
TC X S	2	4.29	0.77	2	0.30	0.02
CNS X TC X S	2	10.34	1.85	2	3.53	0.62
Hormone/Synthetic Substitutes						
Age (covariate)	1	5.13	1.21	1	24.38	1.64
Education (covariate)	1	6.25	1.43	1	0.02	0.01
Hormone/Synthetic Substitutes (HSS)	1	23.45	5.35*	1	1.06	0.07
Training Condition (TC)	2	20.91	4.77*	2	0.16	0.01
Sex (S)	1	30.62	6.98*	1	2.14	0.14
HSS X TC	2	10.61	2.42	2	8.80	0.59
HSS X S	1	42.38	9.67*	1	17.90	1.20
TC X S	2	7.29	1.66	2	9.55	0.64
HSS X TC X S	2	15.44	3.52*	2	14.82	1.00

Note. $^{*}p < 0.05$.

Time 1 compared with if the participant was taking a cardiovascular drug at Time 2). All of these correlations were extremely stable, with correlations approaching $\varphi = 1$. Given this stability, participants' Time 1 data were used in the analyses. It should be noted that the following analyses address how the stable use of particular classes of medications is related to cognitive performance, which is in contrast to the previous analyses that examined change in total number of medications.

Cardiovascular Drugs

The results of the ANCOVA examining the effect of taking at least one cardiovascular drug on the change in the performance on the Letter Series Test (Blieszner et al., 1981) revealed no differences between participants who were taking a cardiovascular drug (M = 1.17, SD = 2.22) compared to those who did not (M = 1.43, SD = 2.72). In addition, the effects of training condition and sex were not significant.

In contrast, there was a significant effect of taking a cardiovascular drug when examining the change in scores on the EPT (Willis & Marsiske, 1997). Specifically, participants taking a cardiovascular drug also displayed a mean increase in scores from the pretest to the 18-month post-test (M = 0.94, SD = 3.41), while those not taking a cardiovascular drug displayed a mean decrease in EPT scores (M = −1.00, SD = 3.79). The effects of sex and training condition were not significant.

Central Nervous System Agents

Analyses examining the change in Letter Series Test scores revealed no significant effects of taking CNS agents, training condition, or sex on inductive reasoning performance, covarying for age and education.

Regarding EPT change scores, ANCOVA analyses revealed no significant main effects for taking a CNS agent, training condition, or sex on cognitive performance. However, a significant interaction was found between sex and use of CNS agents. Simple effects analyses revealed that females taking CNS agents (mean change = −2.08, SD = 3.96) performed significantly worse compared with females who did not take CNS agents (mean change = 0.89, SD = 4.16), $F(1, 67) = 4.05$, $p < 0.05$. There was no significant simple drug effect for males, $p > 0.05$.

Hormone/Synthetic Substitutes

Due to the potential differences between hormones and other synthetic substitutions, separate analyses were performed for participants prescribed hormones and those prescribed other synthetic medications. The pattern of results for those reporting prescription hormone use was identical to the results from the entire subsample who reported taking any drug from this category (n = 29). However, no significant findings were evident for the participants who reported taking only a nonhormonal drug from this category ($n = 5$), which was likely due to the test being extremely underpowered. The results that are reported reflect participants taking any drug from this category.

The results of the ANCOVA revealed a significant effect of taking hormone/synthetic substitutes, as well as significant effect of training condition and sex on change in Letter Series Test scores. However, these main effects were qualified by significant Drug × Sex × Training Condition interaction. Simple interaction analyses indicated that the simple interaction between taking hormones and training condition was significant for females, $F(2, 66) = 12.03$, $p < 0.01$, but not for males, $p > 0.05$. The simple simple effects analyses revealed a training condition effect for female participants taking a hormone/synthetic substitute, $F(2, 66) = 4.09$, $p < 0.05$, and for those that did not take this type of drug, $F(2, 66) = 8.83$, $p < 0.05$. See Figure 1 for the results of the simple comparison analyses. With regard to males, simple effects analyses revealed a simple effect for training condition, $F(2, 66) = 4.04$, $p < 0.05$, and for whether the participants were taking a hormone/synthetic substitute or not, $F(1, 66) = 9.44$, $p < 0.01$ (see Figure 1).

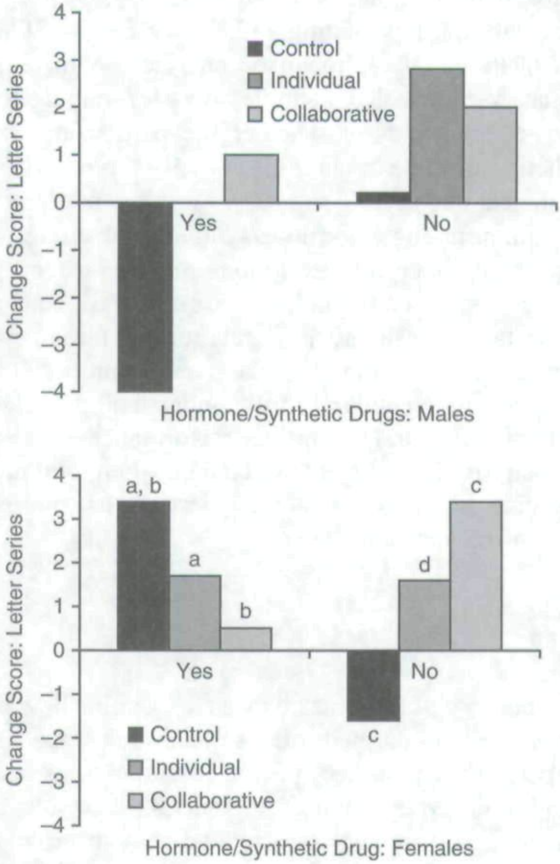
Regarding the change in EPT scores, no significant effects were found for sex, condition, or taking a hormone/synthetic substitute.

In summary, the number of prescriptions and drug category was related to change in scores on an inductive-reasoning task and an everyday problem-solving task. However, these relations differed across the three medication categories, indicating that the overall number of drugs people take may not be sensitive enough to fully understand the relation between prescription medication and cognitive performance. It should also be noted that the pattern of results did not change when total number of prescriptions was entered as a covariate, suggesting that the results are not merely an issue of polypharmacy.

DISCUSSION

The primary purpose of this research was to examine how both the number and types of prescription medications older adults take were related to the change in performance on two specific cognitive tasks (everyday problem solving and inductive reasoning). In general, the results indicated that change in cognitive performance was related to both the number of prescriptions and specific drug classification, and differed by the cognitive measure being analyzed. Each of these findings is discussed in turn.

FIGURE 1. Simple Interactions of Drug × Training Condition × Sex, Broken Down by Sex. For males, the simple interaction was not significant. The simple main effects of Drug and Training were both significant, with follow-up tests indicating that the participants in the individual condition scored higher than the control group and that males taking hormone/synthetic drugs scored lower than those who did not. For females, the simple-simple interaction was significant, with simple-simple effect analyses indicating a Training Condition effect in females who were and were not taking synthetic drugs. Note that bars with the same letters above them were significantly different (e.g., within females not taking this type of drug, the control group significantly differed from the collaborative training condition).



Somewhat surprisingly, an increase in the total number of reported medications was positively related to an increase in scores on both cognitive measures over the 18-month follow-up period. This finding is inconsistent with the extant literature which generally reports that greater medication use is related to poorer cognitive performance (e.g., Meador, 1998; Starr et al., 2004). However, much of the past research has relied on data collected from institutionalized or ill older adults who are at higher risk for polypharmacy, whereas the data in this study were provided by healthy, well educated, community-dwelling older adults. Thus, rather than the number of medications representing health, *per se*, the number of prescriptions may be a proxy for such protective factors as access to health care (Stuart & Grana, 1998), attitude toward health care, or increased awareness of health-related risk factors that may have deleterious effects on cognition (e.g., hypertension). Additionally, there may be a threshold, which the participants in this study did not reach, at which increased prescription use may be detrimental to cognitive performance.

Next, we examined the relation between specific prescription category and change in two measures of cognitive performance. Consistent with past literature, a protective effect of cardiovascular drugs was found, but only for performance on the everyday cognition measure. In the present sample, the use of cardiovascular drugs offered some protection against a decline on an executive functioning task assessing everyday functional ability (Allaire & Marsiske, 2002), but not on a measure that assessed a more basic cognitive ability, namely inductive reasoning.

The results from the hormone/synthetic substitutes analyses indicated varying effects depending on the cognitive measure. The use of hormone/synthetic substitutes was not related to change in performance on more complex everyday problem-solving tasks. However, with regard to the inductive reasoning measure, the three-way interaction between sex, training condition, and whether or not participants were taking hormone/synthetic substitutes indicated that taking hormone/synthetic substitutes had a negative effect for men regardless of training condition. In contrast, for females taking hormone/synthetic substitutes the direction of the effect was different depending on the training group to which they were assigned. The finding that females in the control group benefited from taking hormone/synthetic substitutes is consistent with the literature suggesting a protective role of such drugs as estrogen (e.g., Resnick et al., 1997). However, additional research is needed to disentangle the interaction between the training condition and taking hormone/synthetic substitutes. Within a larger sample reporting more varied prescriptions, analyses examining more specific subclasses of hormone/synthetic substitutes could further clarify this relation. Caution must be taken in interpreting these results, however, due to the relatively small number of males taking hormone/synthetic substitutes and the lack of knowledge regarding the reasons that the participants were taking a drug from this category, which may be quite different for males and females.

Finally, the results for CNS agents suggested that these medications can have different effects depending on the measure of cognitive performance being used. Consistent with past research (Francis et al., 1990), taking CNS agents had a negative effect on cognitive performance, but this relation was only found for females. However, it should be noted that this finding may be due to the relatively low number of males reporting taking a CNS agent (7.5%) and the resulting loss of power. These results are further qualified by the broad range of medications that fall under this category, some of which have different effects on cognitive performance. However, this does not necessarily discount the finding that CNS agents have a differential influence on specific components of cognitive performance. Future research with a larger sample could clarify the relations between specific CNS agents and induction reasoning and everyday problem solving.

Due to the differential findings across the two cognitive measures, the results of this study support the use of more domain-specific cognitive measures when examining potential effects of prescription medications. In addition, when examining the relation between prescription drug usage and cognitive performance, category-specific classifications appear to be more sensitive measures of prescription use compared to sole reliance on the total number of medications.

Considerations and Future Directions

Several issues should be considered when interpreting the findings in this study. First, it is possible that cognitive performance may have been influenced by either the drug itself or the alleviation of symptoms the drug is designed to treat (e.g., the actual chemistry of an antihypertensive drug versus the lowering of one's blood pressure). Longitudinal data collected before the onset of symptoms would be needed to assess the validity of this hypothesis. Second, it is possible that the interactions of the drugs were responsible for the results given that 49% of the sample was taking a combination of drugs. Although the sample size in this study was too small to provide sufficient power to test hypotheses related to drug interactions, it should be noted that entering the total number of drugs as a covariate did not change the results of the medication category analyses in any meaningful way. Relatedly, this study focused on only three categories of prescriptions. However, these three categories were the most commonly reported in the study sample and other categories were not adequately represented for statistical analyses. It is also possible that drug usage served as a proxy for other protective or risk factors such as access to health care or change in health behaviors following a diagnosis of an illness or disorder. Finally, although the focus of this study was use of prescription medication, over-the-counter (OTC) drugs may also influence cognitive performance. Future research should include an in-depth investigation of the influence of all types of medications, including OTC drugs.

A further consideration is the generalizability of the sample. As this sample was relatively healthy and community dwelling, the results add more information regarding noninstitutionalized, well older adults to the existing literature. However, a number of other factors related to cognitive performance, such as depression, anxiety, and presence of certain chronic illnesses, were not assessed. In addition, this sample did not include any minorities, which decreases the generalizability to additional populations.

In terms of future investigations, this research could continue in several directions. First is the comprehensive examination of the effects of change in medication usage, which may include either how the change in the number of prescriptions within each class is related to cognitive performance over time, or the trajectory of medication effects (e.g., Are cognitive effects strongest when the person begins taking a medication?). Relatedly, it may be of value to examine the issue of how actual adherence to prescriptions influences cognitive performance. Dosing issues (e.g., prescribed dose, patient adherence) likely play an important role. A second line of future research is the examination of the effects of specific medication subtypes within each major category. For example, this would entail looking at specific types of cardiovascular medications (e.g., antihypertensives). These types of fine-grained analyses necessitate a larger and more varied sample than what was analyzed in this study.

Although not a primary focus of the current study, it is interesting to note that prescription medications played a role in explaining change in cognitive performance above the influence of training condition. More research is needed to examine the impact of prescription usage on cognitive interventions aimed at older adults. For example, cognitive interventions may serve to increase medication adherence as well as accuracy of medication usage (e.g., dosage, timing). Future research might examine how these effects play out differently over the course of an intervention protocol.

CONCLUSIONS

The results of this study have several implications that bridge basic and applied geriatric practice. First, clinicians should consider medication usage when making clinical and/or cognitive diagnoses due to the demonstrated association between prescription medications and cognitive performance (both basic and more everyday abilities). Second, long-term care providers should be aware of the various effects of prescription medications on different levels of cognitive performance and be observant of any changes in the behavior of older adult patients. Third, clinical psychologists and therapists must be careful when introducing a treatment that may be cognitively demanding with older adults due to possible cognitive impairment related to medication use. Finally, researchers need to account for medication usage (both number and type) when assessing cognitive performance in older adults. This is particularly true for older adults who are taking a number of medications or those who have added or dropped prescriptions during the course of a study.

Overall, the results of this study support the use of specific cognitive measures in the examination of the potential effects of prescription drugs on both basic and higher-level cognitive performance, as well as the continued study of the varying effects of drug class (e.g., cardiovascular, central nervous system agents, and hormones) on cognition for men and women. Furthermore, because the existing literature is equivocal in its findings regarding the cognitive effects of prescription drugs, the results of this study suggest that the use of more specific measures of cognitive performance and category-specific measures of medications might better elucidate the relation between prescription drugs and cognition.

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